ORIGINAL ARTICLE

Blood Storage Duration and Biochemical Recurrence of Cancer After Radical Prostatectomy

Juan P. Cata, MD; Eric A. Klein, MD; Gerald A. Hoeltge, MD; Jarrod E. Dalton, MA; Edward Mascha, PhD; Jerome O'Hara, MD; Amanda Russell, MD; Andrea Kurz, MD; Shamgar Ben-Elihayhu, PhD; and Daniel I. Sessler, MD

OBJECTIVE: **To test the hypothesis that perioperative transfusion of allogeneic and autologous red blood cells (RBCs) stored for a prolonged period speeds biochemical recurrence of prostate cancer after prostatectomy.**

PATIENTS AND METHODS: **We evaluated biochemical prostate cancer recurrence in men who had undergone radical prostatectomy and perioperative blood transfusions from July 6, 1998, through December 27, 2007. Those who received allogeneic blood transfusions were assigned to nonoverlapping "younger," "middle," and "older" RBC storage duration groups. Those who received autologous RBC transfusions were analyzed using the maximum storage duration as the primary exposure. We evaluated the association between RBC storage duration and biochemical recurrence using multivariable Cox proportional hazards regression.**

RESULTS: **A total of 405 patients received allogeneic transfusions. At 5 years, the biochemical recurrence–free survival rate was 74%, 71%, and 76% for patients who received younger, middle, and older RBCs, respectively; our Cox model indicated no significant differences in biochemical recurrence rates between the groups (*P*=.82; Wald test). Among patients who received autologous transfusions (n=350), maximum RBC age was not significantly associated with biochemical cancer recurrence (*P*=.95). At 5 years, the biochemical recurrence–free survival rate was 85% and 81% for patients who received younger and older than 21-day-old RBCs, respectively.**

CONCLUSION: **In patients undergoing radical prostatectomy who require RBC transfusion, recurrence risk does not appear to be independently associated with blood storage duration.**

***Mayo Clin Proc.* 2011;86(2):120-127**

PSA = prostate-specific antigen; RBC = red blood cell

Prostate cancer is the most common malignant neoplasm in men, and radical prostatectomy is among the primary therapies for localized prostate cancer. The biochemical recurrence rate 5 years after prostatectomy ranges from 70% to 90%.[1,2] Improvements in the surgical technique have decreased the amount of intraoperative blood loss occurring during radical prostatectomy[3]; however, substantial numbers of patients still require perioperative blood transfusions.[4-6]

Blood transfusions are associated with adverse reactions, including postoperative infections and transfusion-related immune perturbations.[7,8] Allogeneic leukocytes present in the transfused blood are thought to suppress host cellular immune responses.[9,10] Furthermore, the immunodepressant effect is secondary to an imbalance of accumulated cytokines and proinflammatory mediators in the transfused blood against decreased production of lymphocyte stimulating cell-mediated cytokines, such as interleukin 2,[9,10] and increased release of immunosuppressive prostaglandins in the patient undergoing transfusion.[11,12]

In cancer patients, perioperative blood transfusion has long been suspected of reducing long-term survival,[4,13] but available evidence is inconsistent. It is also unclear which components of transfused blood underlie the cancer-promoting effects reported by some studies.[14,15] An important factor associated with the deleterious effects of blood transfusion is the storage age of the transfused blood units.[16] A recent study using 2 animal models demonstrated that prolonged storage (>9 days) of transfused red blood cells (RBCs) was a critical deleterious factor.[17] Therefore, it seems likely that cancer recurrence may also be worsened after the transfusion of older blood. No clear cutoff point has been established to define old vs young blood; however, a recent large clinical study defined old blood as RBCs with a storage time longer than 14 days.[18]

We thus evaluated the association between RBC storage duration and biochemical prostate cancer recurrence after radical prostatectomy. Specifically, we tested the hypothesis that perioperative transfusion of allogeneic and autologous RBCs stored for a prolonged period is associated with earlier biochemical recurrence of prostate cancer after prostatectomy.

PATIENTS AND METHODS

After approval from the Cleveland Clinic Institutional Review Board, we identified 1127 men (aged ≥18 years) with prostate cancer who underwent open or laparoscopic

From the Department of Outcomes Research (J.P.C., J.E.D., E.M., A.K., D.I.S.) and Department of General Anesthesiology (J.O., A.R.), Anesthesiology Institute, Glickman Urological and Kidney Institute (E.A.K.), Section of Transfusion Medicine, Department of Clinical Pathology (G.A.H.), and Department of Quantitative Health Sciences (J.E.D., E.M.), Cleveland Clinic, Cleveland, OH; and Department of Psychology, Tel Aviv University, Tel Aviv, Israel (S.B.-E.).

Supported by internal funds and the Joseph Drown Foundation (Los Angeles, CA).

Individual reprints of this article are not available. Address correspondence to Daniel I. Sessler, MD, Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Ave, P77, Cleveland, OH, 44195 (DS@OR.org).

radical prostatectomy at Cleveland Clinic between July 6, 1998, and December 27, 2007, and for whom prostate-specific antigen (PSA) follow-up data were available. Demographic, perioperative, and postoperative follow-up data were obtained from Cleveland Clinic's institutional review board–approved, prospectively maintained localized prostate cancer registry. Prostate-specific antigen was used as a biochemical marker of prostate cancer recurrence after prostatectomy. A PSA value of at least 0.4 ng/mL (to convert to μg/L, multiply by 1.0) followed by another increase was considered biochemical cancer recurrence.[19]

Patients who received a blood transfusion during their prostatectomy-related hospitalization were identified. Blood transfusions were administered intraoperatively and postoperatively according to the clinical judgment of the attending anesthesiologist and surgeon, respectively. The donor type (autologous or allogeneic) and storage duration of transfused RBC units were obtained from the Cleveland Clinic transfusion service data repository. Only autologous units collected preoperatively and stored were included in the analysis; autologous RBCs salvaged intraoperatively, processed, and autotransfused were not included.

Assessment of Blood Storage Duration

Assessing blood storage duration as a treatment is complicated because patients who receive multiple units likely have multiple RBC age exposures but only a single recurrence outcome. The mechanism by which patients receive allogeneic blood is essentially a random process; that is, the age of a given allogeneic unit is largely independent of any patient or surgical characteristics. Furthermore, if a given patient receives multiple allogeneic RBC units during a surgical procedure, the ages of those multiple units are likely independent of one another. In contrast, the need for recovery time after reservation of autologous blood makes the mechanism by which blood age is assigned a more systematic or deterministic process; patients receiving multiple autologous RBC units have an inherently wide distribution of RBC age. Another general difference in these populations is that patients receiving solely allogeneic blood are sicker and require more units than those who receive solely autologous blood (in our patients, the median [quartiles] number of units transfused was 2 [2-4] for those who received allogeneic blood but 2 [1-2] for those who received autologous blood).

Because of the differing natures of RBC age exposure between the 2 patient populations, we needed to tailor separate analysis plans for patients who received allogeneic blood vs those who received only autologous blood. We endeavored to define the most meaningful patient-specific RBC age exposure for each population. Assuming that old blood is truly harmful, then the unit of maximum age associated with each patient may be most relevant. However, the more units a patient receives, the less likely it may be that any 1 unit has a significant effect on the patient's prognosis. When patients receive few RBC units, as was the case with patients receiving autologous blood (45% of patients received 1 and 53% received 2 units), the unit of maximum age was of greater relevance to the hypothesis of old blood being associated with increased recurrence. Therefore, for patients who received only autologous blood, we analyzed the maximum RBC age associated with each patient, while adjusting for the range of RBC age exposures as a covariable.

In contrast, 29 of the patients receiving allogeneic blood received 4 or more units, making the unit of maximum age plausibly less relevant. Thus, we assigned patients who received only allogeneic blood to 1 of 3 RBC age exposure groups on the basis of the terciles (ie, the 33rd and 66th percentiles) of the overall distribution of RBC storage duration if *all* their transfused units could be loosely characterized as of "younger," "middle," or "older" age. Although this approach resulted in the removal of certain patients with wide RBC age distributions, it has the advantage of defining an essentially random and clearly separable exposure.

Specifically, we analyzed 3 groups of patients receiving only allogeneic blood: those for whom all transfused units were aged 13 days or less, 13 to 18 days, or 18 or more days. Patients whose blood age distribution straddled a tercile were not included in the study, whereas patients whose blood age distribution lay entirely on a tercile (eg, all units transfused to a particular patient were aged exactly 13 days) were randomly allocated to one of the neighboring blood age groups. The relationship between RBC age and risk of biochemical recurrence was then evaluated (after adjusting for any effects of the covariables described in the "Statistical Analyses" section) using the median RBC age of all transfused units within each group (the younger group had a median age of 10 days; the middle group, 15 days; and the older group, 25 days) as a continuous predictor. A confirmatory analysis that treated RBC age group as a categorical predictor was also performed.

Statistical Analyses

The treatments under study—namely, RBC age group for the analysis in patients given allogeneic RBCs and maximum RBC age for the analysis within patients given autologous RBCs—were assessed univariably using Kaplan-Meier survival density estimation and multivariably using Cox proportional hazards regression. For the multivariable analyses, the number of covariables we could include in our

TABLE 1. **Summary of Demographic, Baseline, and Prognostic Factors by RBC Age Group Among 316 Patients Undergoing Prostatectomy With Allogeneic-Only Transfusion Strategy**[a]

Factor	RBC age group			*P* value
	Younger (n=106)	Middle (n=103)	Older (n=107)	
Year of treatment	02 (00-07)	02 (00-05)	03 (01- 06)	.78
Age (y)	61±7	62±7	60±8	.45
African American race	18 (17)	18 (17)	19 (18)	.99
Family history of disease	23 (22)	17 (17)	28 (26)	.23
Prostate volume (g)	49 (41-67)	53 (43-64)	47 (38-62)	.16
Tumor volume				.72
Low	17 (17)	23 (23)	24 (22)	
Medium	53 (51)	46 (46)	54 (50)	
Extensive	33 (32)	31 (31)	29 (27)	
Clinical T category				.25
T1-T2a	88 (85)	90 (93)	91 (88)	
T2b-T3	15 (15)	7 (7)	12 (12)	
Biopsy Gleason score				.36
0-6	58 (55)	65 (64)	66 (62)	
7	39 (37)	26 (26)	28 (26)	
8-10	9 (8)	10 (10)	13 (12)	
Bladder neck positive	7 (7)	6 (6)	5 (5)	.83
Organ confined[b]	64 (60)	67 (65)	76 (71)	.26
Preoperative PSA (ng/mL)[c]	6 (5, 8)	6 (5, 9)	6 (5, 10)	.19
Preoperative therapy	13 (12)	12 (12)	13 (12)	.99
No. of allogeneic units	2 (2, 3)	2 (2, 2)	2 (1, 2)	.02
Surgical Gleason score				.30
NA	13 (12)	12 (12)	13 (12)	
NR, 0-6	23 (22)	33 (32)	29 (27)	
7	66 (62)	48 (47)	58 (54)	
8-10	4 (4)	10 (10)	7 (7)	
Any adjuvant therapy[d]	2 (2)	1 (1)	4 (4)	.38
Adjuvant radiation therapy	1 (1)	0 (0)	0 (0)	.37

[a] *P* values from one-way analysis of variance for normally distributed continuous variables (presented as mean ± SD), Kruskal-Wallis one-way analysis of variance by ranks for non–normally distributed continuous variables (presented as median [quartiles]), and Pearson χ^2 test for categorical variables (presented as number [%] of patients). NA = surgical Gleason score not assigned because of neoadjuvant therapy; NR = no residual disease or negative pathology report; PSA = prostate-specific antigen; RBC = red blood cell.

[b] *Organ confined* is defined as at least one of the following diagnoses: extracapsular extension, seminal vesicles, margin, or positive lymph nodes.

[c] SI conversion factor: To convert ng/mL to μ/L, multiply by 1.0.

[d] Including hormones, chemotherapy, or orchiectomy.

TABLE 2. **Association Between Various Baseline Demographic and Prognostic Factors and Maximum Autologous RBC Storage Duration for 350 Patients Undergoing Prostatectomy**[a]

Factor	Correlation (95% CI) with maximum RBC age	*P* value[b]
Year of treatment	0.02 (–0.08-0.13)	.68
Age	0.07 (–0.03-0.18)	.18
Prostate volume	0.01 (–0.10-0.12)	.87
Preoperative PSA	–0.01 (–0.12-0.09)	.84
Number of autologous units	0.17 (0.06-0.27)	.002

Factor	Maximum RBC age (d), mean (SD)	*P* value[c]
Race		.17
African American	20.2 (6.6)	
Other	22.3 (7.4)	
Family history		.38
No	22.4 (7.3)	
Yes	21.5 (7.6)	
Tumor volume		.92
Low	22.5 (7.4)	
Medium	22.1 (7.6)	
Extensive	22.1 (7.0)	
Clinical T category		.03
T1-T2a	22.4 (7.3)	
T2b-T3	17.7 (4.8)	
Biopsy Gleason score		.34
0-6	22.4 (7.4)	
7	21.9 (7.1)	
8-10	19.7 (8.3)	
Bladder neck positive		.16
No	22.2 (7.4)	
Yes	18.3 (4.7)	
Organ confined		.23
No	21.2 (7.2)	
Yes	22.4 (7.4)	
Preoperative therapy		.70
No	22.1 (7.3)	
Yes	22.9 (10.2)	
Surgical Gleason score		.28
NA	22.9 (10.2)	
7	21.6 (6.9)	
8-10	24.0 (6.6)	
0-6	23.0 (7.9)	
Adjuvant therapy[d]		.46
No	22.1 (7.4)	
Yes	24.6 (1.7)	
Adjuvant radiation therapy		.37
No	22.2 (7.4)	
Yes	20.2 (5.7)	

[a] CI = confidence interval; NA = surgical Gleason score not assigned because of neoadjuvant therapy; PSA = prostate-specific antigen; RBC = red blood cell.

[b] *P* value testing the null hypothesis of zero correlation (Fisher z test).

[c] *P* value from one-way analysis of variance F test.

[d] Including hormones, chemotherapy, or orchiectomy.

models was limited because of the small number of recurrences observed in our patients (ie, 54 recurrences among the patients receiving allogeneic blood and 37 among those receiving autologous blood). Thus, we adjusted for clinical T category, number of units transfused, and any other factors listed in Table 1 and Table 2 that were univariably significant with the respective exposure at the $P<.20$ significance criterion.

The assumption of proportional hazards between treatment groups for each Cox model was assessed by including an interaction (assessed at the .10 significance level) between logarithm on time and the corresponding treatment. Also, for the patients receiving allogeneic RBCs, we conducted the following sensitivity analyses. First, we relaxed the linear trend assumption and analyzed RBC age group as a categorical predictor. Second, in light of the relatively large proportion of patients lost to follow-up within 2 years

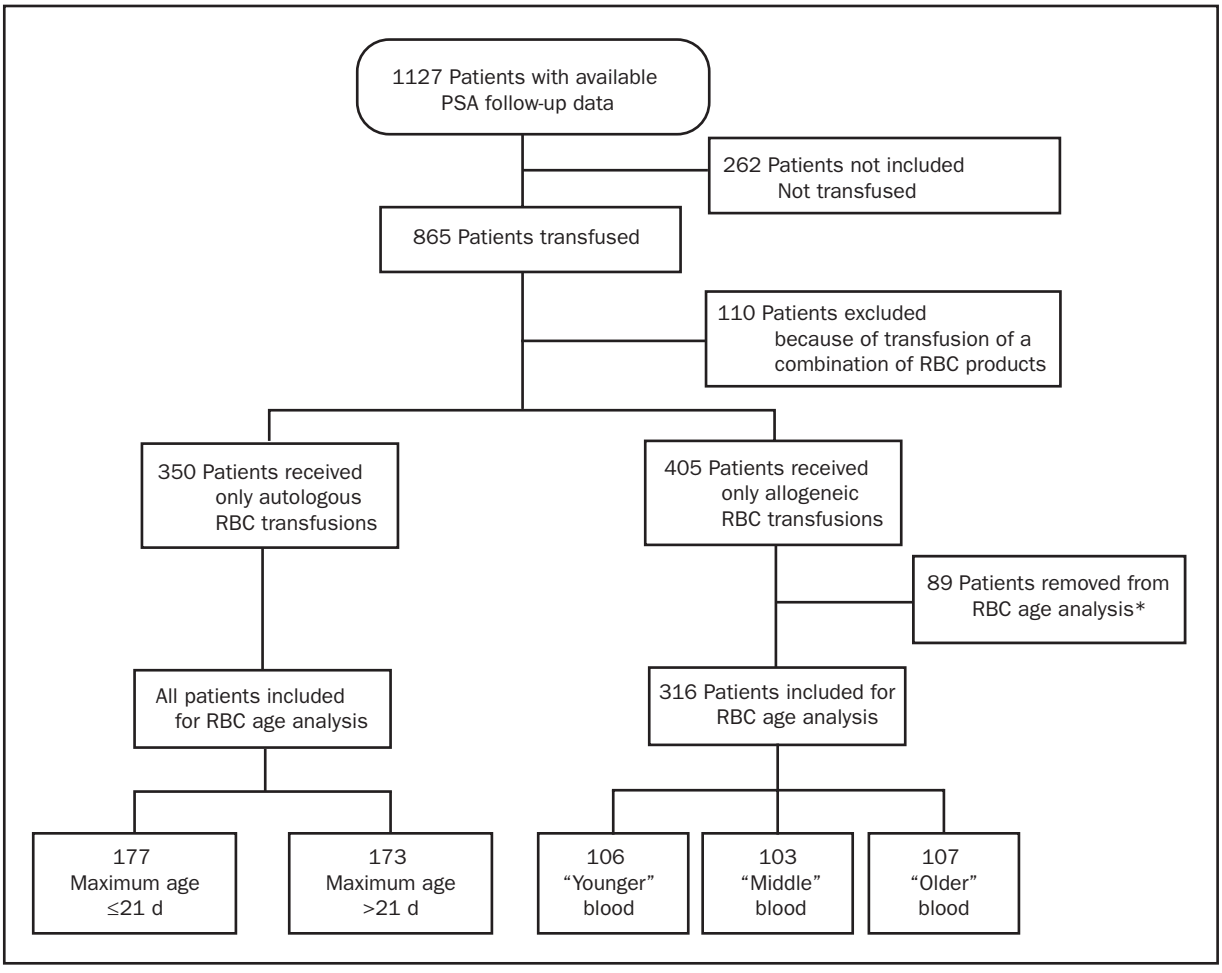

FIGURE 1. Summary of patients included in the study. Asterisk indicates that these patients received a combination of "younger," "middle," and "older" allogeneic red blood cells (RBCs). PSA = prostate-specific antigen.

of surgery (see "Results" section), we performed an unadjusted analysis that included only those patients with recurrence or with more than 2 years of follow-up. Finally, we assessed whether those excluded for receiving a combination of younger, middle, and older RBC units (as defined in the "Assessment of Blood Storage Duration" section) differed on biochemical recurrence–free survival from those included in the primary analysis.

Overall, our study had 90% power at the overall .05 significance level to detect hazard ratios of 2.62 or greater when comparing allogeneic-only RBC age groups and a hazard ratio of 1.71 or greater for a relative increase in maximum storage duration of 7 days among patients who received only autologous blood.

SAS statistical software, version 9.2 (SAS Institute, Cary, NC) and R statistical software, version 2.8.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for the analysis.

RESULTS

The initial population consisted of 1127 men who had undergone radical prostatectomy at Cleveland Clinic and had available PSA follow-up data. Of these patients, 865 received transfusion during or within 30 days of the surgical procedure. Of the transfused patients, 110 were excluded from the analysis because they received a combination of allogeneic and autologous blood products. Of the remaining 755 patients, 405 (54%) received solely allogeneic and 350 patients (46%) received solely autologous RBC units (Figure 1).

Association Between Storage Duration of Allogeneic Transfused RBC Units and Cancer Recurrence

Of the 405 patients who received allogeneic RBC transfusion, 89 (22%) were excluded because their transfused RBC age distribution included more than one of the ter-

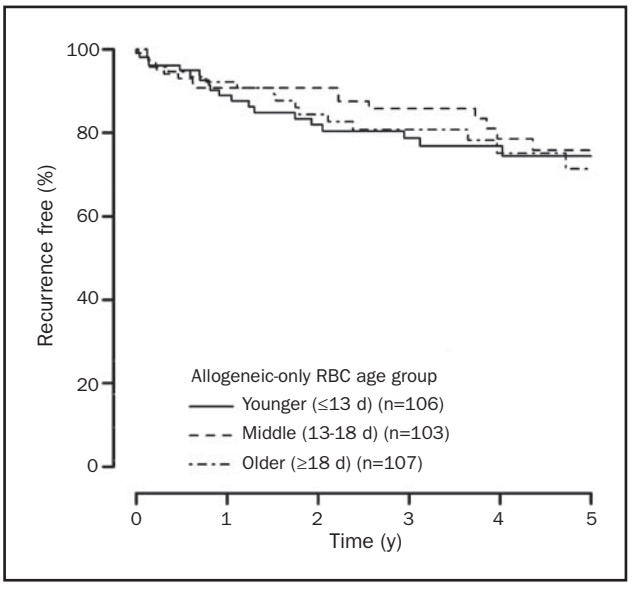

FIGURE 2. Kaplan-Meier survival density function estimates comparing patients who received only allogeneic blood who were grouped according to red blood cell (RBC) storage duration exposure. Univariable survival estimates were not significantly different (*P*=.97, log-rank test); multivariate *P*=.29.

ciles. Of the remaining 316 patients, 106 (34%) had all younger blood, 103 (33%) had middle blood, and 107 (34%) had older blood. A total of 776 allogeneic units were transfused; patients in the younger group received 275 units (35%), those in the middle group received 234 units (30%), and patients in the older group received 267 units (34%). The median (quartiles) number of units transfused per patient for the younger, middle, and older RBC age groups, respectively, was 2 (2-3), 2 (2-2), and 2 (1-2) (*P*=.02, Kruskal-Wallis one-way analysis of variance by ranks; Table 1). Of the 316 patients, 119 (38%) were lost to follow-up within 2 years of the date of the surgical procedure but were included in the survival analysis. The proportion of patients lost to follow-up for the 3 respective RBC age groups was 36%, 41%, and 37%.

The estimated 1-year biochemical recurrence–free survival rate (95% confidence interval [CI]) for the younger, middle, and older groups was 89% (82-95), 92% (86-98), and 91% (85-97), respectively. At 5 years, these survival rates were 74% (64-85), 71% (58-84), and 76% (64-87). Kaplan-Meier survival density function estimates showed that survival was not univariably different (*P*=.97, log-rank test) (Figure 2).

In our Cox model, we adjusted for prostate volume and preoperative PSA (in addition to clinical T category and number of RBC units transfused); 23 patients (7%) were excluded from the model because of missing covariable values. On the basis of this model, the linear slope parameter for RBC age, derived using the 3 group-specific median storage durations as a continuous predictor, was not statistically significant (*P*=.82, Wald χ^2 test).

Using the estimated linear slope parameter, we estimated the hazard ratio (Bonferroni-adjusted 95% CI) for recurrence at 0.98 (0.76-1.26) when comparing patients in the middle storage duration group with the younger group, at 0.95 (0.57-1.58) when comparing the older group with the middle group, and at 0.93 (0.43-1.98) when comparing the older group with the younger group. The interaction between logarithm on time and the linear slope parameter representing storage duration was not statistically significant (*P*=.90), indicating no violation of the proportional hazards assumption between the RBC age groups. Our confirmatory analysis, which treated RBC age group as a categorical predictor, revealed similarly nonsignificant results (*P*=.95, Wald test).

In our sensitivity analyses, we found no evidence of nonlinearity in the association between RBC age and biochemical recurrence (*P*=.80, Wald test for categorical RBC age group predictor); all CI estimates from the model assuming a linear trend were entirely within the CI estimates from the model using the categorical RBC age group treatment. In our unadjusted analysis, which excluded those with less than 2 years of follow-up, we had consistent results with our primary model (*P*=.82, Wald test). Finally, we found no evidence of differing biochemical recurrence rates between those whose blood could be characterized as younger, middle, or older (on the basis of our previously described criteria) and the 89 not included because their transfused RBC age distribution overlapped one or both of the terciles (*P*=.15, Wald test).

Association Between Storage Duration of Autologous Transfused RBC Units and Cancer Recurrence

The 350 patients given only autologous blood were divided into 2 groups according to the overall median autologous patient-specific RBC age of 21 days (quartiles of 17 and 28 days) for the purposes of univariable Kaplan-Meier estimation. The estimated 1-year biochemical recurrence–free survival rate (95% CI) for patients who received younger and older than 21-day-old RBCs was 96% (93%-99%) and 98% (95%-100%), respectively. At 5 years, the biochemical recurrence–free survival rate was 85% (77%-92%) and 81% (72%-90%) for patients who received younger and older than 21-day-old RBCs, respectively. The proportion of patients receiving only autologous blood who were lost to follow-up within 2 years of prostatectomy was 37%.

We found no statistically significant univariable relationship between autologous RBC age group and recurrence (Figure 3; log-rank, *P*=.88). Overall, there were 37 recurrences among the 350 patients receiving autologous

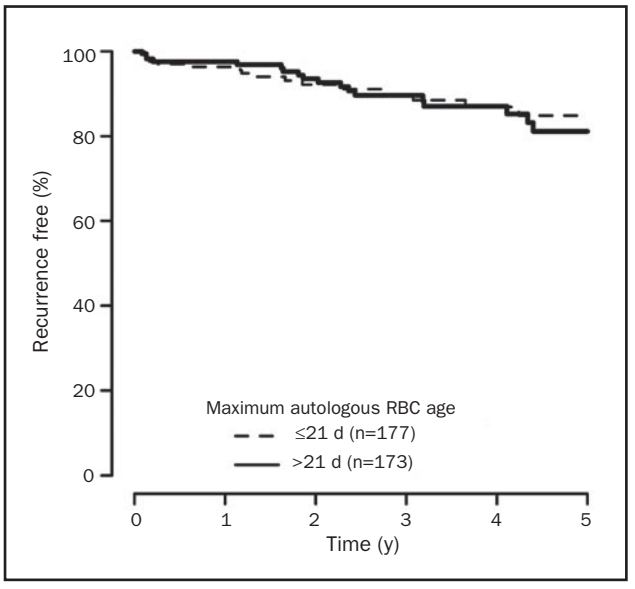

FIGURE 3. Kaplan-Meier survival density function estimates comparing patients who received only autologous blood who were grouped according to patient-specific maximum red blood cell (RBC) storage duration. For Kaplan-Meier estimation purposes only, patients whose maximum RBC age was equal to or less than the median of 21 days were assigned to the "younger" group and patients whose maximum RBC age was greater than the median were assigned to the "older" group. Univariable survival estimates were not significantly different (P=.87, log-rank test); multivariable P=.14 (using maximum RBC age as a continuous predictor variable).

RBCs; this small number of recurrences limited the number of predictors that we could include in our Cox model (one parameter per 10 events is standard practice for avoiding model overfitting). Thus, we included the 2 most significant covariables in our Cox model evaluating maximum RBC age; these were number of units and clinical T category. After adjustment for these variables, maximum RBC age was not significantly associated with recurrence; the estimated hazard ratio for a difference of 7 RBC age days was 0.99 (95% CI, 0.72-1.35; P=.95). We could not test for violation of the proportional hazards assumption in this model because of the small number of recurrences.

DISCUSSION

Red blood cells undergo *storage lesion* as their storage time increases. This term refers to the metabolic, structural, and biochemical changes that RBCs undergo between collection and transfusion,[20-22] with most of these changes occurring after the second or third week of storage.[23] In patients undergoing rectal surgery, blood storage age is associated with postoperative infectious complications.[24]

We evaluated one potential consequence of the storage lesion. Specifically, we investigated the effect of RBC storage on the rate of prostate cancer recurrence and were unable to demonstrate a significant association between storage age and cancer recurrence for either allogeneic or autologous transfusion. These findings were unexpected because a growing number of publications suggest that outcomes are unfavorable after transfusion of RBCs with prolonged storage age,[25-28] although there is by no means a consensus regarding the effect of blood storage age on cancer recurrence.[29,30]

Gao et al[31] demonstrated the presence of circulating prostate cancer cells in the peripheral blood obtained from patients with prostate cancer immediately before prostatectomy. Therefore, the perioperative period is critical in the cancer disease process because any immunosuppressive intervention may facilitate formation of micrometastases. Allogeneic or autologous blood transfusions per se may trigger an abnormal immune response, which may be caused by soluble modifiers released from leukocytes into the supernatant fluid of RBCs, allogeneic mononuclear cells, or HLA class I peptides.[23,32] Regulatory T cells promote immune tolerance, prevent autoimmunity, suppress cell-mediated cytotoxicity, and inhibit the function of dendritic cells.[33-35] Baumgartner et al[36] demonstrated that the supernatant from stored peripheral RBCs induced regulatory T cells; however, the induction was not affected by the storage age of the RBCs. Blood transfusions may impair the natural immune-killing function of the body against growing and metastasizing cancer cells.[26-28,37] Ectosomes are microparticles or microvesicles released from the membrane of erythrocytes and are present in the packaged RBCs. Interestingly, ectosomes also cause immunosuppression by inhibiting activated macrophages.[38]

Early preclinical studies showed that transfusion of allogeneic whole blood promoted the growth of fibrosarcoma cells in syngeneic C57BL/6 mice and of the VX-2 tumor cell line in rabbits.[39,40] The authors of these studies suggested that effects of allogeneic blood transfusion were due to the presence of white cells in the transfused blood. Moreover, it has been suggested that CD 200^+ and $CD11^+$ dendritic cells present in transfused blood are responsible for inducing tumor growth in animals inoculated with cancer cells.[41] Leukoreduction of stored RBCs has less of a significant effect on cancer growth stimulation compared with administration of nonleukoreduced RBCs.[17] However, even administration of leukoreduced blood is associated with cancer growth[17]; therefore, it is possible that the presence of other soluble factors related to storage may still cause significant immunosuppression or stimulate cancer cell growth.[38] In a more recent animal study, Atzil et al[17] showed that transfusion of either allogeneic or autologous blood stored for more than 9 days increased lung tumor retention and reduced survival rates compared with either

no transfusion or treatment with blood of a shorter storage duration. Importantly, these effects were ascribed to deterioration of RBCs, rather than to white blood cells or accumulating soluble factors.[17]

The clinical evidence of the effect of blood storage age on cancer recurrence is less clear than the evidence in animal models. For example, Edna and Bjerkeset[29] found that blood storage time had no effect on local recurrences and distant metastases in 336 patients who had colorectal resective cancer surgery. However, Mynster and Nielsen[30] demonstrated that, compared with patients who did not undergo transfusion, those who received allogeneic blood stored for less than 21 days had increased locoregional cancer recurrence after colorectal surgery, whereas those who underwent transfusion with blood with a storage age older than 21 days had a recurrence rate similar to that of nontransfused patients. However, there are substantial differences between these studies and ours, which limits direct comparisons. For example, the type of malignant tumor differed, as did the definitions of storage duration (ie, median vs nonoverlapping tercile splits).

Our study had several limitations. First, the results of any retrospective study, including ours, may be influenced by confounding factors. However, we used multivariable regression models and found a reasonably balanced distribution of known confounding factors within our patients. We used median or tercile splits to define storage duration groups. Others have used various definitions, which makes it difficult to directly compare our findings with other reports. Second, we did not analyze the effect of other perioperative comorbidities related to blood transfusions, such as postoperative infection, which had been suggested as playing a role in the postoperative rate of cancer recurrence.[42] Furthermore, we did not analyze the effect of any blood transfusion vs no blood transfusion on cancer recurrence. In a meta-analysis, Amato and Pescatori[43] showed a detrimental association between the use of blood transfusion and outcome in patients with colorectal cancer. In our study, because of a current change in surgical technique among our surgeons, we did not focus on whether or not patients underwent blood transfusions. During the past 5 years, more prostatectomies were accomplished laparoscopically vs open, and as a result of this experience and improved perioperative management of these patients, surgeons have become aware of risks and costs associated with transfusions. Third, we found that a large percentage of patients underwent transfusion in the perioperative period. A similar rate of transfusion was reported by Paul et al,[44] who found that 56.7% of the patients undergoing retropubic radical prostatectomy received transfusions intraoperatively or postoperatively. However, a study from Mayo Clinic demonstrated that the rate of transfusion was strikingly smaller than ours; therefore, our results may not be applicable across other academic centers.[45]

Finally, a substantial limitation we faced was statistical power, which was restricted by the number of patients available in our registry; thus, our negative conclusions hardly eliminated the possibility of clinically important effects related to type of blood, leukocyte filtering, or RBC storage duration.

CONCLUSION

Administration of allogeneic and autologous RBCs with increased storage time is not associated with the biochemical recurrence of prostate cancer after radical prostatectomy. Thus, available data do not suggest that, with respect to cancer recurrence, special efforts should be expended to transfuse patients undergoing radical prostatectomy with RBCs stored only briefly.

We thank Alwyn Reuther (statistician and data manager, Urological Institute, Cleveland Clinic) for her valuable technical assistance.

REFERENCES

1. Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15-year Johns Hopkins experience. *Urol Clin North Am*. 2001;28(3):555-565.

2. Zincke H, Bergstralh EJ, Blute ML, et al. Radical prostatectomy for clinically localized prostate cancer: long-term results of 1,143 patients from a single institution. *J Clin Oncol*. 1994;12(11):2254-2263.

3. Acharya SS, Zorn KC, Shikanov S, et al. Evolution of open radical retropubic prostatectomy: how have open surgeons responded to the challenge of minimally invasive surgery? *J Endourol*. 2009;23(11):1893-1897.

4. Gonzalgo ML, Pavlovich CP, Trock BJ, Link RE, Sullivan W, Su LM. Classification and trends of perioperative morbidities following laparoscopic radical prostatectomy. *J Urol*. 2005;174(1):135-139.

5. Touijer K, Eastham JA, Secin FP, et al. Comprehensive prospective comparative analysis of outcomes between open and laparoscopic radical prostatectomy conducted in 2003 to 2005. *J Urol*. 2008;179(5):1811-1817.

6. Ou YC, Yang CR, Wang J, Cheng CL, Patel VR. Comparison of robotic-assisted versus retropubic radical prostatectomy performed by a single surgeon. *Anticancer Res*. 2009;29(5):1637-1642.

7. Klein HG. Immunomodulatory aspects of transfusion: a once and future risk? *Anesthesiology*. 1999;91(3):861-865.

8. Vamvakas EC. Why have meta-analyses of randomized controlled trials of the association between non-white-blood-cell-reduced allogeneic blood transfusion and postoperative infection produced discordant results? *Vox Sang*. 2007;93(3):196-207.

9. van Twuyver E, Mooijaart RJ, ten Berge IJ, et al. Pretransplantation blood transfusion revisited. *N Engl J Med*. 1991;325(17):1210-1213.

10. Jensen LS, Andersen AJ, Christiansen PM, et al. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg*. 1992;79(6):513-516.

11. Francis DM. Relationship between blood transfusion and tumour behaviour. *Br J Surg*. 1991;78(12):1420-1428.

12. Chung M, Steinmetz OK, Gordon PH. Perioperative blood transfusion and outcome after resection for colorectal carcinoma. *Br J Surg*. 1993;80(4):427-432.

13. Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: fact or fiction? *Blood*. 2001;97(5):1180-1195.

14. Houbiers JG, Brand A, van de Watering LM, et al. Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. *Lancet*. 1994;344(8922):573-578.

15. van de Watering LM, Brand A, Houbiers JG, Klein Kranenbarg WM, Hermans J, van de Velde C. Perioperative blood transfusions, with or without allogeneic leucocytes, relate to survival, not to cancer recurrence. *Br J Surg*. 2001;88(2):267-272.

16. Eickhoff JH, Gote H, Baeck J. Peri-operative blood transfusion in relation to tumour recurrence and death after surgery for prostatic cancer. *Br J Urol*. 1991;68(6):608-611.

17. Atzil S, Arad M, Glasner A, et al. Blood transfusion promotes cancer progression: a critical role for aged erythrocytes. *Anesthesiology*. 2008;109(6): 989-997.

18. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*. 2008;358(12):1229-1239.

19. Stephenson AJ, Kattan MW, Eastham JA, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. *J Clin Oncol*. 2006;24(24):3973-3978.

20. Chin-Yee I, Arya N, d'Almeida MS. The red cell storage lesion and its implication for transfusion. *Transfus Sci*. 1997;18(3):447-458.

21. Tinmouth A, Chin-Yee I. The clinical consequences of the red cell storage lesion. *Transfus Med Rev*. 2001;15(2):91-107.

22. Sparrow RL, Veale MF, Healey G, Payne KA. Red blood cell (RBC) age at collection and storage influences RBC membrane-associated carbohydrates and lectin binding. *Transfusion*. 2007;47(6):966-968.

23. Berezina TL, Zaets SB, Morgan C, et al; Danish RANX05 Colorectal Cancer Study Group. Influence of storage on red blood cell rheological properties. *J Surg Res*. 2002;102(1):6-12.

24. Mynster T, Nielsen HJ. The impact of storage time of transfused blood on postoperative infectious complications in rectal cancer surgery. *Scand J Gastroenterol*. 2000;35(2):212-217.

25. Weinberg JA, McGwin G Jr, Griffin RL, et al. Age of transfused blood: an independent predictor of mortality despite universal leukoreduction. *J Trauma*. 2008;65(2):279-282.

26. Hoh H, Umpleby H, Cooper A, Taylor I. Recurrence of colorectal cancer and perioperative blood transfusion: is blood storage time important? *Dis Colon Rectum*. 1990;33(2):127-130.

27. Vamvakas EC. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. *Transfusion*. 1995;35(9):760-768.

28. Dionigi G, Rovera F, Boni L, et al. The impact of perioperative blood transfusion on clinical outcomes in colorectal surgery. *Surg Oncol*. 2007;16(suppl 1):S177-S182.

29. Edna TH, Bjerkeset T. Perioperative blood transfusions reduce long-term survival following surgery for colorectal cancer. *Dis Colon Rectum*. 1998;41(4):451-459.

30. Mynster T, Nielsen HJ. Storage time of transfused blood and disease recurrence after colorectal cancer surgery. *Dis Colon Rectum*. 2001;44(7):955-964.

31. Gao CL, Rawal SK, Sun L, et al. Diagnostic potential of prostate-specific antigen expressing epithelial cells in blood of prostate cancer patients. *Clin Cancer Res*. 2003;9(7):2545-2550.

32. Vamvakas EC. Possible mechanisms of allogeneic blood transfusion-associated postoperative infection. *Transfus Med Rev*. 2002;16(2):144-160.

33. Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. *Blood Rev*. 2007;21(6):327-348.

34. Dieckmann D, Plottner H, Berchtold S, Berger T, Schuler G. Ex vivo isolation and characterization of CD4(+)CD25(+) T cells with regulatory properties from human blood. *J Exp Med*. 2001;193(11):1303-1310.

35. Tang Q, Bluestone JA. The Foxp3+ regulatory T cell: a jack of all trades, master of regulation. *Nat Immunol*. 2008;9(3):239-244.

36. Baumgartner JM, Silliman CC, Moore EE, Banerjee A, McCarter MD. Stored red blood cell transfusion induces regulatory T cells. *J Am Coll Surg*. 2009;208(1):110-119.

37. Berardi R, Brunelli A, Tamburrano T, et al. Perioperative anemia and blood transfusions as prognostic factors in patients undergoing resection for non-small cell lung cancers. *Lung Cancer*. 2005;49(3):371-376.

38. Sadallah S, Eken C, Schifferli JA. Erythrocyte-derived ectosomes have immunosuppressive properties. *J Leukoc Biol*. 2008;84(5):1316-1325.

39. Blajchman MA, Bardossy L, Carmen R, Sastry A, Singal DP. Allogeneic blood transfusion-induced enhancement of tumor growth: two animal models showing amelioration by leukodepletion and passive transfer using spleen cells. *Blood*. 1993;81(7):1880-1882.

40. Bordin JO, Bardossy L, Blajchman MA. Growth enhancement of established tumors by allogeneic blood transfusion in experimental animals and its amelioration by leukodepletion: the importance of the timing of the leukodepletion. *Blood*. 1994;84(1):344-348.

41. Clark DA, Gorczynski RM, Blajchman MA. Transfusion-related immunomodulation due to peripheral blood dendritic cells expressing the CD200 tolerance signaling molecule and alloantigen. *Transfusion*. 2008;48(5):814-821.

42. Hirai T, Yamashita Y, Mukaida H, Kuwahara M, Inoue H, Toge T. Poor prognosis in esophageal cancer patients with postoperative complications. *Surg Today*. 1998;28(6):576-579.

43. Amato AC, Pescatori M. Effect of perioperative blood transfusions on recurrence of colorectal cancer: meta-analysis stratified on risk factors. *Dis Colon Rectum*. 1998;41(5):570-585.

44. Paul R, Schmid R, Busch R, et al. Influence of blood transfusions during radical retropubic prostatectomy on disease outcome. *Urology*. 2006;67(1): 137-141.

45. Nuttall GA, Cragun MD, Hill DL, et al. Radical retropubic prostatectomy and blood transfusion. *Mayo Clin Proc*. 2002;77(12):1301-1305.